Intensive Care Med
https://doi.org/10.1007/s00134-025-07933-x

WHAT'S NEW IN INTENSIVE CARE

Acute kidney injury: when and how to start renal replacement therapy

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Acute kidney injury (AKI) affects up to 50% of patients admitted to the intensive care unit (ICU), and is associated with a higher risk of mortality and progressive kidney disease. Renal replacement therapy (RRT) is initiated in a substantial minority of critically ill patients with AKI yet debate persists about when and how RRT should be deployed. We synthesize the latest research and provide nuanced recommendations about the prescription of RRT for the management of AKI in the ICU.

When to initiate RRT

Situations not requiring immediate RRT: AKI without life-threatening complications

The debate on optimal RRT timing has been informed by several randomized controlled trials [1–5]. The overarching message from these trials is that the initiation of RRT in the absence of a life-threatening complication, even in the presence of KDIGO stage 2 or 3 AKI, does not confer a survival benefit. A delayed strategy can enable avoidance of RRT in up to 50% of patients, thanks to a spontaneous improvement in renal function observed in most cases. In the one trial that demonstrated an advantage of earlier RRT initiation [5], many of the patients had volume overload, a common trigger for RRT initiation, at the time of enrolment. As such the interpretability of the results is challenging.

There were no subgroups of patients who seemed to particularly benefit from earlier RRT. On the contrary, a strategy of early RRT initiation may lead to excess mortality in the absence of oligo-anuria [6] and may increase the risk of long-term dialysis dependence, particularly in patients with pre-existing chronic kidney disease [7]. Greater exposure to RRT may compromise kidney repair and the return of endogenous kidney function, possibly mediated by RRT-associated hemodynamic instability.

The lack of benefit of earlier RRT in the aforementioned trials should not be interpreted as an endorsement of unlimited RRT deferral in patients with unremitting AKI. Notably, patients in the delayed arms of those trials who initiated RRT did so at a median of 31–57 h from enrolment [1, 3, 4]. As such, the safety of delaying RRT beyond this threshold is unclear. The AKIKI-2 trial [2] compared a strategy of "delayed" RRT initiation, which entailed the commencement of RRT 72 h after the onset of Stage 3 AKI, to a "more delayed" strategy, which constituted further deferral of RRT. The "more delayed" strategy did not lead to more RRT-free days and there was a signal towards higher mortality. Moreover, in comatose patients with severe AKI, a more delayed RRT initiation strategy resulted in a lower chance of transitioning from coma to awakening [8].

Managing AKI-related complications and defining triggers for RRT initiation

There is general agreement that immediate RRT initiation is indicated for patients with life-threatening complications, such as severe hyperkalemia, profound metabolic acidosis, and significant fluid overload. However, there is significant variability in the thresholds chosen to consider metabolic complications and fluid overload to be "life-threatening". In the absence of a high level of evidence, we provide below some practical guidance for the management of these patients.

To date, there are no randomized controlled studies comparing different strategies according to the severity

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of hyperkalemia. In the previously cited studies investigating the timing of RRT, the trigger for RRT initiation was set at serum potassium values between 5.5 and 6.5 mmol/L. Diuretics (if there is concomitant volume overload) and novel potassium binders may be useful adjuncts in the management of hyperkalemia and thus facilitate the deferral of RRT.

More extensive data exist on the management of metabolic acidosis. In patients with metabolic acidosis (pH ≤ 7.20) and AKI (KDIGO stage 2–3) [9], treatment with sodium bicarbonate may reduce mortality and the need for RRT. Adjunctive therapies like sodium bicarbonate can temporarily stabilize patients with severe acidemia, but RRT should not be delayed if pH remains < 7.20 after administration of 250 mL of 4.2% sodium bicarbonate.

Fluid overload is the most challenging of the "urgent RRT indications" to define objectively. Physical exam assessments are challenging, and quantitative assessments of fluid overload (e.g. % fluid overload) may not be a reliable reflection of volume status. Bedside ultrasound and bioimpedance are non-invasive tools that may complement more traditional data to define volume status and guide therapy. At present, the decision to initiate RRT due to fluid excess requires the careful integration of physical exam findings, fluid balance data, radiographic images the patient's oxygenation status and ultimately, clinician judgement.

How to initiate RRT

Choosing the RRT modality

Once the decision to initiate RRT has been made, the question arises as to which modality to use (intermittent or continuous), and this has been a longstanding debate. To date, large RCTs have found no significant difference in survival [10]. However, it remains controversial whether the preferential use of CRRT may confer better kidney outcomes among survivors. Recently, two secondary analyses of large RCTs [1, 3, 4] found conflicting results. In the first, IHD compared to CRRT as the first modality was associated with greater 60-day survival in patients with less severe disease (SOFA score < 10) [11]. In the second, CRRT as the first modality was associated with a lower risk of death and RRT dependence at 90 days, compared with the initial receipt of IHD. This association was predominantly driven by a lower risk of RRT dependence at 90 days [12].

Other RRT prescription settings

For patients receiving CRRT, current standards recommend delivering CRRT with a small molecule clearance rate of 20–25 mL/kg/h [13]. It is unclear if a lower clearance rate confer comparable outcomes and this is the subject of several ongoing trials (NCT06014801, NCT06021288, NCT06446739). There is also evidence to show that regional anticoagulation of the extracorporeal circuit with citrate, as compared to heparin, leads to longer filter life with a lower risk of bleeding [14]. It remains unclear whether hemofiltration, which provides enhanced removal of larger-sized molecules through convection, confers superior outcomes to hemodialysis, which relies on diffusive clearance [15]. Finally, the rate of ultrafiltration remains a controversy. While more aggressive fluid removal may help achieve euvolemia more rapidly, this comes at the cost of hemodynamic instability [16]. Ongoing research programs are assessing optimal ultrafiltration strategies in critically ill patients with AKI (NCT06071026, NCT05473143).

Conclusion and clinical recommendations

When to initiate RRT for AKI in ICU

For most patients, in the absence of urgent clinical indications, a strategy of RRT deferral and watchful waiting is preferable. The timing of initiation is probably not related to survival, but later initiation may lead to RRT avoidance in some patients. However, in patients with unresolving AKI (i.e. persistent oliguria and/or BUN > 112 mg/dL), waiting more than 72 h after the onset of Stage 3 AKI may be harmful, even in the absence of classic life-threatening complications (Fig. 1).

How to initiate RRT for AKI in ICU

Regarding RRT modality, the choice between IHD and CRRT depends on the patient's hemodynamic status and the specific clinical needs. CRRT is believed to be more suitable for patients receiving inotropes or pressors and/or with significant volume overload, whereas IHD is likely a safe alternative for patients with less severe disease. This recommendation is not supported by strong evidence and relies on usual practice. Current CRRT standards recommend a delivered RRT dose of 20–25 mL/kg/h and regional citrate anticoagulation over heparin for anticoagulation of the extracorporeal circuit. The choice between hemofiltration and hemodialysis remains unclear, and the optimal ultrafiltration rate is still debated. Ongoing trials will hopefully shed light on these controversies.

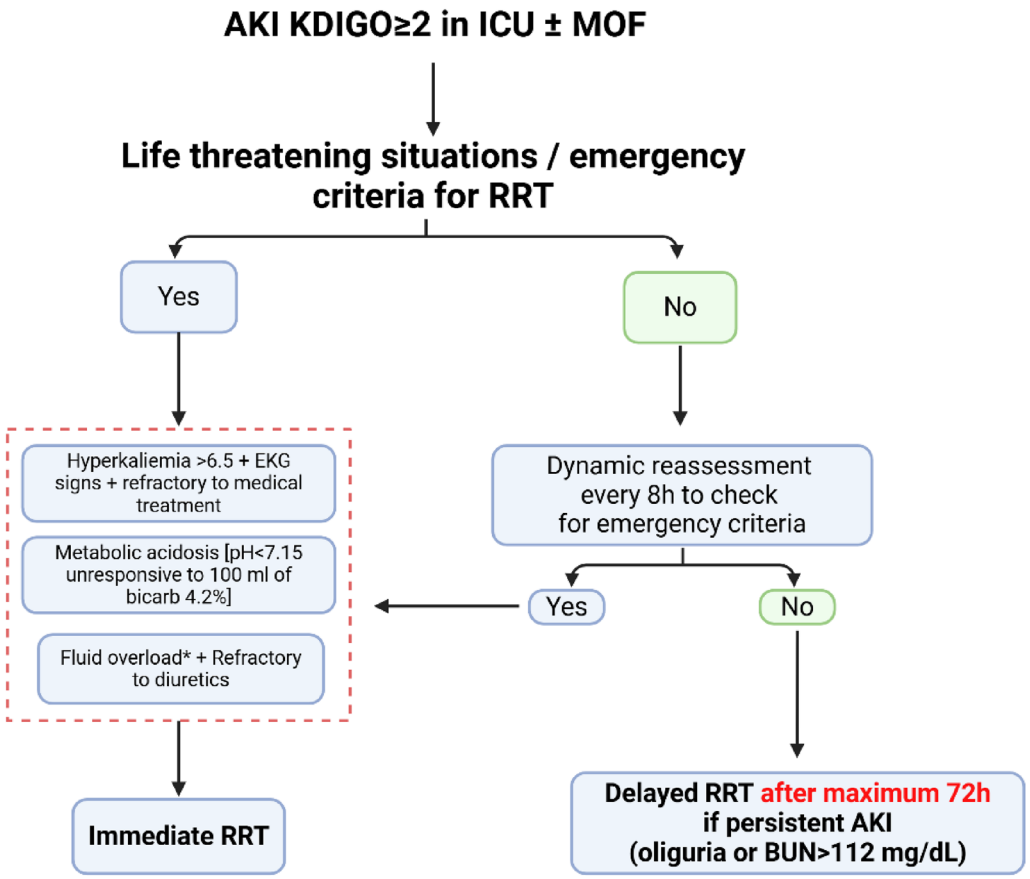
AKI KDIGO≥2 in ICU ± MOF
Life threatening situations / emergency criteria for RRT
Yes
No
Hyperkaliemia >6.5 + EKG signs + refractory to medical treatment
Metabolic acidosis [pH<7.15 unresponsive to 100 ml of bicarb 4.2%]
Fluid overload* + Refractory to diuretics
Dynamic reassessment every 8h to check for emergency criteria
Yes
No
Immediate RRT
Delayed RRT after maximum 72h if persistent AKI (oliguria or BUN>112 mg/dL)

Fig. 1 Practical algorithm to guide decision-making about when and how to initiate renal replacement therapy in the management of acute kidney injury in the intensive care unit. *AKI* acute kidney injury, *ICU* intensive care unit, *MOF* multiorgan failure, *RRT* renal replacement therapy, *CKD* chronic kidney disease, *SOFA* sequential organ failure assessment, *CRRT* continuous renal replacement therapy, *IHD* intermittent hemodialysis. *Worsening pulmonary oedema, paO_2/FiO_2 < 200 mmHg or fluid balance > 10% of body weight

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Data availability
Not applicable

Declarations

Conflicts of interest
The authors declare that they have no conflicts of interest relevant to this article.

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Received: 12 February 2025 Accepted: 29 April 2025
Published online: 19 May 2025

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